IN THE UNITED STATES PATENT OFFICE
BOARD OF PATENT APPEALS & INTERFERENCES

#39
1071
JRP
9/14/04

In re Application of W. Roy KNOWLES, M.D.

Docket No. _____
Application No. 09/619,142
filed 19 July 2000

REPLY BRIEF

REPLY BRIEF

This REPLY BRIEF is submitted in response to the 1 July 2004 SUPPLEMENTAL EXAMINER'S ANSWER.[1]

RELATED APPEALS AND INTERFERENCES

Contrary to what the EXAMINER'S ANSWER says, an appeal is pending.

Applicant first filed its APPEAL in this case on April 26, 2001. The Examiner refused to file an EXAMINER'S ANSWER for several years.

Applicant accordingly petitioned the Court of Appeals for the Federal Circuit for relief. On June 16, 2004, the Court ordered the Director for Patents to appear in Court and explain the Examiner's refusal. *See* In re Knowles at 2 (Docket No. Misc. 767, 16 June 2004) (copy enclosed). Two weeks later, the Examiner filed her ANSWER.

Curiously, that ANSWER says, "The court, however, denied the mandamus petition and dismissed any appeal to the CAFC." *See* EXAMINER'S ANSWER at 3.

This is baldly incorrect. An appeal is pending before The Federal Circuit. *See* In re Knowles (Docket No. Misc. 767, 16 June 2004) (copy enclosed).

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[1] N.B.: While the paper is styled a "SUPPLEMENTAL" ANSWER, it is the first and only ANSWER filed in this case.

9/15/04 We
Of entered : Considered

ISSUES PRESENTED

The EXAMINER'S ANSWER proposes that "the issues should be directed to whether all the critical elements required by the instant claims including the specific concentration as claimed are taught by the cited references." EXAMINER'S ANSWER at 4.

Applicant disagrees. This issue was addressed - and resolved - during the six OFFICE ACTIONS reviewing the dozens of references of record in this case. The Office has already conceded that the references as a whole do not teach all elements of the instant claims.[2]

Therefore, the issue on appeal is not whether the references teach the instant claims; it is whether, given the factual findings of record in this case, the Office can now allege contradictory facts.[3] Applicant respectfully believes the Office cannot.

GROUPING OF CLAIMS

The APPEAL BRIEF states that the claims are separately patentable.

The Examiner responds that this statement "is not clear." EXAMINER'S ANSWER at 5. The EXAMINER'S ANSWER, however, fails to say exactly what part of Applicant's language is "unclear."

Furthermore, the EXAMINER'S ANSWER itself shows how each claim is separately patentable. For example, the EXAMINER'S ANSWER urges the Board to group claims 1, 2 and 3 together. The EXAMINER'S ANSWER then concedes claim 2 is patentable over GIBSON; claim 3 is patentable over ZUPAN, and claims 1 and 3 are patentable over the SCHOSTAREZ combination. The EXAMINER'S ANSWER thus concedes that claims 1, 2 and 3 are separately patentable. The Board is therefore respectfully believed to lack the legal power to group the claims as the Examiner urges.

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[2] As a related matter, the EXAMINER'S ANSWER says that it "supercedes any previous office action." EXAMINER'S ANSWER at 2. This is incorrect. The EXAMINER'S ANSWER elaborates on, but cannot as a matter of law "supercede," the previous six OFFICE ACTIONS.

[3] The statement of Issues Presented provides an example of contradictory facts. The EXAMINER'S ANSWER says, "the limitation recited in the preambles (i.e. penetration to a depth of approximately the depth of hair bulbs) is considered to be an inherent feature which would naturally be achieved when the concentration of the penetration enhancer as claimed is met." EXAMINER'S ANSWER at 4. Three years ago, the Examiner conceded that this factual assertion is incorrect, and withdrew *en toto* the rejections relying on it. *See* OFFICE ACTION (28 Sept. 2001) at 2.

PRIOR ART OF RECORD

The EXAMINER'S ANSWER relies on art different from that relied on in the most recent OFFICE ACTION.

The EXAMINER'S ANSWER relies on MIKULAK *et al.*, 50(2) J. PHARM. PHARMACOL. 153 (1998) (abstract only); ORENTREICH, United States Letters Patent No. 5,053,403[4]; and RAJADHYAKSHA, United States Letters Patent No. 5,482,965[5]. These three references were made of record several years ago. When Applicant pointed out their deficiencies, the Office conceded their failings. They are thus not mentioned in the most recent (20 Feb. 2003) OFFICE ACTION.

ARGUMENT

The EXAMINER'S ANSWER Shows
Why the Section 112 Rejection
Must Be Withdrawn

The EXAMINER'S ANSWER withdraws the 35 U.S.C. 112 objection.[6]

The EXAMINER'S ANSWER establishes undisputed factual findings which show the Section 112 rejection must be withdrawn as a matter of law.

The only support for the Section 112 rejection is that "there is no pertinent teaching of retinoid penetration enhancer(s) ... in the original disclosure." EXAMINER'S ANSWER at 6, ¶ 10(a).

While this may be true, it is not a basis for a Section 112 rejection. The original disclosure need not teach retinoid penetration enhancer. The original dsclosure *should not* teach this. Office procedure expressly discourages including this. The Specification should preferably omit material already known in the art. MPEP § 2164.01, *citing* In re Buchner, 929 F.2d 660,

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[4] EXAMINER'S ANSWER at 8.
[5] EXAMINER'S ANSWER at 15.
[6] The OFFICE ACTION (20 Feb. 2003) raised both a rejection and an objection under 35 U.S.C. 112. Office procedure says that when "there has been both a rejection and objection by the examiner, the [objection] becomes appealable and should not be decided by petition." MPEP (Feb. 2003) at § 2163.06(II). In the immediate case, while both the rejection and objection must be argued in an appeal, the EXAMINER'S ANSWER fails to object. Thus, the objection has been withdrawn.

661 (Fed. Cir., 1991) ("A patent need not teach, and preferably omits, what is well-known in the art.").

In the immediate case, the EXAMINER'S ANSWER alleges that retinoid penetration enhancers were known in the art. Because the Office alleges that retinoid penetration enhancers were known in the art, the Specification need not expressly teach this. *See* id. The Examiner's demand that Applicant do so is contrary to the Office's own procedure. *See* id.

Furthermore, the undisputed factual record shows the claims are allowable. Negative claim limitations are proper as long as "the boundaries of the patent protection sought are set forth definitely, albeit negatively." In re Barr, 444 F.2d. 588, 595 (C.C.P.A. 1971).[7] In the immediate case, the EXAMINER'S ANSWER says, "it would not be difficult to measure the scope of the claimed invention." EXAMINER'S ANSWER at 16. The EXAMINER'S ANSWER concedes that the boundaries of the protection sought are set forth definitely.

Therefore, the Section 112 rejection must be withdrawn.

BAZZANO

The EXAMINER'S ANSWER alleges facts which show that BAZZANO cannot anticipate the claims as a matter of fact.

BAZZANO Expressly Teaches Away from the Claimed Invention

BAZZANO teaches away from the claimed combination. APPEAL BRIEF at 9. The EXAMINER'S ANSWER does not dispute this.

Rather, the EXAMINER'S ANSWER says that BAZZANO "is capable of performing the intended use." EXAMINER'S ANSWER at 14. As support, the EXAMINER'S ANSWER cites to BAZZANO at column 20, lines 54 *et seq*. The cited text, however, fails to support the Examiner. It says, "for retinoic acid 1 mg/kg body weight/day is a maximal dose which will eventually cause toxicity and with chronic treatment *will probably cause the hair to fall out*." Id. at col. 54, line 64 to col. 55, line 1 (emphasis added).

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[7] *See also*, All Dental Prodx, LLC v. Advantage Dental Prods., Inc., 309 F.3d 774 (Fed. Cir. 2002) (a specification adequately complies with 35 U.S.C. 112, first paragraph, whenever it is reasonably clear what the invention is); In re Wakefield, 422 F.2d 897, 904 (C.C.P.A. 1970) (negative claim limitations can be used to "exclude the characteristics of prior art products.").

BAZZANO says long-term use of retinoic acid will "probably cause the hair to fall out." BAZZANO itself says it is not "capable of performing the intended use."

In contrast, the claimed invention requires a non-retinoid penetration enhancer. The claimed combination - unlike BAZZANO's retinoid combination - has been shown to be unexpectedly effective, even in long-term use. *See* SPECIFICATION at page 12, line 6 to page 14, line 7.

BAZZANO fails to teach every limitation *of the claims*

The EXAMINER'S ANSWER fails to allege that BAZZANO teaches *every limitation* of the claims. The EXAMINER'S ANSWER says that BAZZANO "teaches a method of treating alopecia." EXAMINER'S ANSWER at 7. This fails to state a *prima facie* case that BAZZANO teaches *the claimed* method.

The EXAMINER'S ANSWER points to BAZZANO at column 3, lines 60-65 and claim 13. That text says:

> According to the invention it has been found that retinoids or mixtures thereof in combination with minoxidil and/or minoxidil-type compounds are synergistically effective in stimulating or increasing the rate at which hair grows on mammalian skin, prolonging the anagen phase of the hair cycle, converting vellus hair to terminal growth hair, and treating alopecias due to organic dysfunction of the hair follicle by topical application

Id. at column 13, lines 60-65. This teaches retinoid combined with minoxidil. This fails to teach "non-retinoid penetration enhancer" as is required by the claims. Claim 13 does no better, and also - as the Examiner has previously conceded - fails to *enable practicing* the claimed invention.

Progesterone

The art teaches that progesterone is not acceptable for the claimed combination. The Office has already conceded this, and withdrew the rejections raised in Paper No. 5.

The Examiner now tries to re-litigate this same argument. *See* EXAMINER'S ANSWER at 8, *citing* Paper No. 5 (OFFICE ACTION (31 Oct. 00)). This is illegal.

The record includes the following factual findings:

ORENTREICH teaches the topical use for hair loss of progesterone. ORENTREICH says progesterone has systemic side effects so serious that it should not be systemically administered for hair loss. ORENTREICH says, "The serious side effects (such as decreased libido) produced by the systemic administration of antiandrogens precludes the systemic use of these drugs for the treatment of the above skin disorders. For example, progesterone is a highly active 5α reductase enzyme inhibitor, but systematically disturbs the menstrual cycle in women." Id. at col. 1 lines 45-51. ORENTREICH concludes that cardiac arrhythmias, feminization and impotency are side effects generally **not acceptable** for treating hair loss. ORENTREICH says these side effects **preclude systemic use** of these compounds for skin disorders. Id. at col. 1, lines 45-52. The Office has already conceded the correctness of the forgoing.

HOKE, United States Letters Patent No. 5,994,319, teaches that progesterone and minoxidil are unacceptable for hair loss. HOKE teaches that progesterone has severe adverse systemic effects like "feminization or impotency." Id. at col. 4 lines 18-23.

HOKE teaches that minoxidil doesn't work. Id. at col. 3, lines 4-11 ("only 8% of patients reported a dense re-growth of scalp hair"). HOKE also teaches that minoxidil has "potent" cardiovascular side effects. Id. at col. 3 lines 4-14. HOKE says minoxidil is "a potent anti-hypertensive" cardiac drug. HOKE says that systemic use of minoxidil can risk cardiac arrhythmias. HOKE at col. 5, line 4-6. HOKE teaches that minoxidil combined with a penetration enhancer may precipitate cardiac arrhythmias. *See* W.R. KNOWLES, *Rule 132 Declaration* at ¶¶3-7, 14-17. Thus, HOKE discourages using minoxidil *at all*, with or without penetration enhancer.[8] Id.

HOKE thus teaches away from the claimed combination of penetration enhancer with minoxidil or a testosterone blocker. The Office has already conceded this.

The claims require penetration enhancer combined with minoxidil or a 5α-reductase inhibitor. HOKE and ORENTREICH thus teach that for hair loss, combining a penetration enhancer with minoxidil or progesterone is not worth the risk. They thus teach away from the

[8] HOKE teaches using his patented nucleotides instead. HOKE says nucleotides are safe because they are "highly selective" genetic binders. They thus do not pose the systemic side effect risk seen with minoxidil or progesterone.

claimed combination. *See* W. Roy KNOWLES, *Rule 132 Declaration* (5 Feb. 2001) at ¶¶ 5-6, 14-17.

The Examiner has already conceded this. *See, e.g.*, OFFICE ACTION (28 Sept. 2001) (withdrawing rejections based on ORENTREICH and HOKE).

BAZZANO Does not Enable The Claimed Invention

BAZZANO actively teaches away from the claimed invention. BAZZANO teaches that systemic minoxidil presents serious cardiac side effect risks. Id. at col. 3 line 49-52; col. line 43-45. BAZZANO says that without added retinoid, *minoxidil does not work.* BAZZANO says:

> Minoxidil is recognized as being somewhat effective in producing new vellus hair growth and sparse terminal hair growth in a pre-selected group of subjects. However, its effect is far from satisfactory in most subjects. * * * minoxidil may not be able to sustain the growth of terminal hairs from the vellus hairs on the scalp. In the majority of subjects with alopecia, terminal hair growth on the scalp may not be initiated or sustained by the topical application of minoxidil nor by its systemic administration.

Id. at col. 3, line 53-56; col. 4, line 49-54. BAZZANO says that without her claimed retinoid compounds, minoxidil lacks any "profound effect" and "cannot" produce a strong response. Id. at col. 5, lines 17 - 42. BAZZANO explains that her claimed retinoids "can initiate cell growth and differentiation (not initiated by minoxidil)" required for hair growth. Id. BAZZANO says minoxidil alone "does not appear to be a sufficient stimulus for hair growth, particularly in an area affected by alopecia." Id. at col. 4, line 63-65.

Thus, BAZZANO teaches away from the claimed combinations. The Applicant - contrary to BAZZANO's teaching - has shown that minoxidil can be used effectively without addition of retinoid.

BAZZANO Does Not Teach Penetration Enhancer

BAZZANO does not teach penetration enhancer.

The Examiner has already admitted this, but quipped that penetration enhancer "is not considered to be critical." OFFICE ACTION at 5 (Oct. 24, 2000). This argument fails because each claim element is, as a matter of law, "critical."

Now, the Examiner now attempts to contradict her earlier factual findings. The EXAMINER'S AMENDMENT alleges that the PEG-ethanol vehicle taught by BAZZANO is a penetration enhancer. This is a misrepresentation of the factual record.

BAZZANO calls PEG-ethanol a "vehicle." The word "vehicle" means "an **inert** substance (as syrup, lard, or liquid petrolatum) in a medicinal compound through which an active agent is administered or by which other ingredients are held together : diluent, excipient." WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY at 2538 (Merriam-Webster Inc., 1986) (emphasis added) (copy attached); *see also* W. Roy KNOWLES, SUPPLEMENTAL DECLARATION at 1 (25 April 2001) (copy attached); SPECIFICATION at pg. 17, line 15-17, pg. 18, line 16 to pg. 19 line 9; 21 C.F.R. § 352.70 (Food & Drug Administration treats PEG as an inert vehicle) (copy attached); *cf.*, F.D.A.-approved product insert (PEG-ethanol used as an inert vehicle for ROGAINE® brand topical minoxidil) (copy attached).

BAZZANO teaches that PEG-ethanol is a "vehicle," an inert substance by definition. *See* WEBSTER'S DICTIONARY at 2538, id.

The EXAMINER'S ANSWER, however, carps that BAZZANO says PEG-ethanol is a "vehicle," not an "inert vehicle." EXAMINER'S ANSWER at 15. This is correct, but irrelevant; a vehicle is by definition inert. There is no need for BAZZANO to say it twice.

The EXAMINER'S ANSWER also says that "Rajadhyaksha[] Mikulak et al[], Zupan(US4440777, col.4, line 37), Gobson(US5015470, col. 14) are provided" to show that PEG-ethanol is a penetration enhancer. EXAMINER'S ANSWER at 15. The record, however, shows the opposite. Neither ZUPAN at col. 4, line 37, nor GIBSON at col. 14 mentions PEG-ethanol at all, much less the specific ratio PEG-ethanol blend used as a vehicle by BAZZANO.

Furthermore, both RAJADHYAKSHA and MIKULAK contradict "the examiner's allegation." This is why the Examiner withdrew reliance on these references two years ago.

RAJADHYAKSHA

RAJADHYAKSHA teaches improved trans-dermal drug delivery agents.

The Examiner has conceded that RAJADHYAKSHA teaches compounds that effectively deliver drugs into the systemic blood circulation. RAJADHYAKSHA at col. 2 line 16-19. The

Examiner has conceded that these compounds pass "through the skin and the systemic circulation" to the liver and yield nontoxic liver metabolites. Id. RAJADHYAKSHA says:

> Typically systemically active agents which may be delivered transdermally are therapeutic agents which are sufficiently potent such that they can be delivered *through the skin or other membranes to the bloodstream* in sufficient quantities to produce the desired therapeutic effect. In general this includes agents in all of the major therapeutic areas including ... cardiovascular preparations including calcium channel blockers, beta-blockers, antiarryhthmics, antihypertensives, diuretics, vasodilators including general, coronary, peripheral and cerebral.

Id. at col.7 line 40-57. "*Systemically active* agents are used in amounts calculated to achieve and maintain *therapeutic blood levels* in a human or other animal." Id. at col. 3 line 53-60; col. 10 line 11-14 (emphasis added).

The Examiner has already conceded that RAJADHYAKSHA thus teaches using compounds for systemic drug delivery. Id. at col. 18 line 1-28. The Examiner has conceded that RAJADHYAKSHA's data show that his compounds do in fact make the drugs penetrate *completely though the skin.* Id. at col. 18 line 55 to col. 19 line 12 and Example 32; *see also*, W.Roy KNOWLES, *Supplemental Declaration.* RAJADHYAKSHA says:

> Typically systemically active agents which may be delivered transdermally are therapeutic agents which are sufficiently potent such that they can be delivered *through the skin or other membranes to the bloodstream* in sufficient quantities to produce the desired therapeutic effect. In general this includes agents in all of the major therapeutic areas including ... cardiovascular preparations including calcium channel blockers, beta-blockers, antiarryhthmics, antihypertensives, diuretics, vasodilators including general, coronary, peripheral and cerebral.

Id. at col. 7 line 40-57.

The Examiner has already conceded that RAJADHYAKSHA does not teach delivering drugs "to the depth of the hair bulbs." To the contrary, the Examiner has already conceded that RAJADHYAKSHA teaches delivering drugs **completely through the skin,** into the systemic bloodstream. Id. at Example 32.

The Examiner has already conceded that RAJADHYAKSHA teaches delivering drugs to the systemic blood stream using a 5% concentration of 5-Amino-5-ethyl-2-(3-heptyl)-1,3-dioxane. Id. at Examples 28-30. The Examiner has already conceded that RAJADHYAKSHA

teaches delivering minoxidil to the blood stream using a 5% concentration of 5-Amino-5-ethyl-2-(3-heptyl)-1,3-dioxane. Id. at col. 15 line 26. (Perhaps because he feared the dangerous cardiac side effects, RAJADHYAKSHA avoided actually doing this example - it is just a prophetic example.)

The Examiner has already conceded that RAJADHYAKSHA teaches, at Example 29, a systemic birth control patch for delivering progesterone to the systemic blood stream. *See also* W. Roy KNOWLES, *Supplemental Declaration.* The Examiner has already conceded that the patch is not used in "alopecia or maintaining healthy hair," nor does it appear to deliver testosterone blocker "to a depth of approximately the depth of hair bulbs." The Examiner has already conceded that for hair loss, RAJADHYAKSHA *teaches away from* combining penetration enhancers of any kind with minoxidil or testosterone blocker, due to adverse systemic side effects. The Examiner has already conceded that RAJADHYAKSHA does not enable the claimed invention. *See also* W. Roy KNOWLES, *Supplemental Declaration.*

The Examiner made these factual findings two years ago. The Office is respectfully believed prohibited from now re-litigating these factual findings.

MIKULAK et al.

MIKULAK *et al.*, 50(2) J. PHARM. PHARMACOL. 153 (1998) (abstract only), discloses a new skin penetration agent called "TPDS."

The record shows the following undisputed factual findings:

The Examiner has already conceded that MIKULAK compares TPDS to two other methods of drug administration. The Examiner has already conceded that MIKULAK compares TPDS to (1) PEG-ethanol as the experimental control, (2) an unnamed, albeit "commonly used" skin penetration enhancer, and (3) oral administration. Id. ("We compared the TPDS with a 50:50 (vol./vol.) mixt. of propylene glycol and ethanol, a commonly used penetration enhancer, and with oral administration."). The Examiner has already conceded that MIKULAK teaches that polyethylene glycol is an (inert) vehicle used as the experimental control, not a skin penetration enhancer.

Furthermore, assuming that MIKULAK's 50:50 PEG-ethanol blend were a penetration enhancer, the Examiner has already conceded that BAZZANO fails to teach the use of such a 50:50 blend.

The Examiner has already conceded the forgoing, and withdrew reliance on MIKULAK. *See, e.g.*, OFFICE ACTION (9 May 2002) (withdrawing rejections based on MIKULAK; OFFICE ACTION (20 Feb. 2003). The Office is respectfully believed bound by its own prior factual findings.

The EXAMINER'S ANSWER now alleges that "Gibson or Zupan specifically exemplifies number of compounds listed as penetration enhancers which shares common chemical structures." EXAMINER'S ANSWER at 16. This assertion is both baseless and incorrect. It is baseless because the record is devoid of any evidence at all showing that the compounds share a "common chemical structure."

It is incorrect because the compounds in fact have widely-divergent chemical structures. For example, GIBSON at col. 14 lists both acetone (C_3H_6O) and diisopropyl sebacate ($C_{36}H_{30}O_4$), compounds which have widely-divergent chemical formulae, as well as structures.

The EXAMINER'S ANSWER Fails to State a *Prima Facie* Case that GIBSON Anticipates

GIBSON, United States Letters Patent No. 5,015,470, teaches inhibiting enzymes which interfere with hair growth.

The EXAMINER'S ANSWER argues that GIBSON "teaches a topical composition for maintaining and increasing hair growth comprising minoxidil and a penetration enhancer." EXAMINER'S ANSWER at 8. As support, the EXAMINER'S ANSWER cites to GIBSON Table 1, the Abstract, and col. 4, lines 40-42. The cited text, however, fails to support the Examiner.

Table 1 compares a topical vehicle (70% ethanol, 20% water and 10% propylene glycol) alone to vehicle containing 2% (w/v) minoxidil. Id. at col. 20, lines 9-26. Table 1 uses PEG-ethanol as the inert experimental control.

The Abstract says, "A composition suitable for topical application to mammalian skin or hair for inducing, maintaining or increasing hair growth compromises: (i) a first chemical inhibitor chosen from proteoglycanase inhibitors, glycosaminoglycanase inhibitors,

glycosaminoglycan chain cellular uptake inhibitors or The Abstract fails to teach a non-retinoid penetration enhancer combined with a testosterone blocker nor minoxidil.

Column 4, lines 40-44 teaches combining minoxidil with a specific kind of penetration enhancer. This text fails, however, to teach nor enable penetration enhancer to deliver testosterone blocker nor minoxidil to the hair bulbs.

The EXAMINER'S ANSWER fails to address the failings in GIBSON which are raised in the APPEAL BRIEF.

GIBSON Combined With BAZZANO and SCHOSTAREZ Does Not Render Obvious The Claimed Invention

The EXAMINER'S ANSWER says the claimed invention is obvious over GIBSON combined with BAZZANO and with SCHOSTAREZ. This rejection must be withdrawn, because the EXAMINER'S ANSWER fails to state a *prima facie* case of obviousness.

A *prima facie* case of obviousness requires the Examiner to identify some suggestion to combine the references. This suggestion to combine must appear somewhere in the art of record. In re Lee, 277 F.3d 1338, 1344 (Fed. Cir., 2002); *cf.* In re Dillon, 919 F.2d 688, 692 (Fed. Cir., 1990) (the suggestion to combine must be in the art of record, albeit the art may teach a use different than the claimed use).

In the immediate case, the EXAMINER'S ANSWER fails to identify any suggestion to combine anywhere in the voluminous references or record. To the contrary, the Examiner concedes that the voluminoius art of record expressly teaches away from making the claimed combination.

For example, SCHOSTAREZ, United States Letters Patent No. 5,373,012, teaches 5-fluoro substituted minoxidil. The Examiner has conceded that SCHOSTAREZ quantifies the cardiac side-effects of each compound, showing that they have similar dose-dependent effects on mean arterial pressure, Fig. 1, and on changes in heart rate, Fig. 2. The Examiner has conceded that SCHOSTAREZ further shows that 5-fluoro substituted minoxidil penetrates completely through the skin and into the systemic blood circulation over three times more quickly than plain minoxidil, *see* SCHOSTAREZ at Table IV - creating three times the incidence of adverse systemic side effects.

In lieu of a suggestion to combine somewhere in the art of record, the EXAMINER'S ANSWER makes a factual assertion which is both baseless and, if true, demonstrates non-obviousness of the combination.

The EXAMINER'S ANSWER says that one would be motivated to combine the references because each component "utilize[es] different biological pathway and potentiat[es] other component's activity." EXAMINER'S ANSWER at 11. The EXAMINER'S ANSWER fails, however, to offer any evidentiary basis for this assertion (*i.e.*, the Examiner fails to allege what the "different biological pathways" involved here are, nor how the references teach these pathways). This allegation cannot be used to reject any claim because it is baseless.

It also directly contradicts the Examiner's previous assertion that the claimed components "have the same biological pathway(working via same mechanism)." OFFICE ACTION at 5 (31 Oct. 2000).

Further, assuming the claim components use "different biological pathways" as the EXAMINER'S ANSWER alleges, this shows the combinations are non-obvious. This is because the Office has already taken the position that similar biological pathways evince a motivation to combine. OFFICE ACTION at 5 (31 Oct. 2000). The Office cannot have it both ways; if similar pathways suggest an obvious combination, then different pathways must suggest a non-obvious combination.

The EXAMINER'S ANSWER also says, "each patentee (Bazzano or Schostarez) teaches that 5 alpha reductase inhibitor ... can be used effectively in combination with minoxidil to improve its antialopecia effects." EXAMINER'S ANSWER at 10. This fails to state a *prima facie* case, because the claimed combination is not 5 alpha reductase inhibitor combined with minoxidil. The claimed combination is *non-retinoid skin penetration enhancer* combined with 5 alpha reductase inhibitor or with minoxidil (or both). The Examiner has already conceded that both BAZZANO and SCHOSTAREZ teach away from combining skin penetration enhancer with 5 alpha reductase inhibitor or minoxidil.

Regarding claims 7-10, 16 and 18-21, it is undisputed that SCHOSTAREZ shows that the 5-flouro compound inherently penetrates through the skin and into the systemic circulation -

precipitating cardiac side effects. It is undisputed that neither SCHOSTAREZ nor GIBSON propose any solution to prevent this.

Nonetheless, the EXAMINER'S ANSWER asserts that "[t]he determination of effective dosage regiments required by [claims 7-10, 16 and 18-21] are considered to be within the level of the ordinary skilled artisan, and because the minor variations including the selection of optimal dosages or variable applications in order to determine the most effective treatment is commonly practiced and obvious." EXAMINER'S ANSWER at 11. Applicant respectfully disagrees, because the art of record teaches the exact opposite.

The art of record does not teach the claimed ratios are "commonly practiced." To the contrary, the art of record teaches against practicing the claimed combination at all, in any ratio. *See. e.g.*, ORENTREICH, HOKE and SCHOSTAREZ (each discussed above), and BRADBURY, PARTIAN and KITA (each discussed in the prior prosecution history and since withdrawn as references). Tellingly, the EXAMINER'S ANSWER fails to say where any reference teaches the claimed ratios. In six OFFICE ACTIONS and an EXAMINER'S ANSWER, the Examiner has never introduced any evidence showing the claimed ratios are known in the art at all, much less "commonly practiced," nor that "selection of an optimal dosage" would have been obvious.

Because the record is devoid of any evidence showing that the specific ratios of claims 7-10. 16 and 18-21 were known in the art at all, the EXAMINER'S ANSWER has failed to state a *prima facie* case of obviousness.

The EXAMINER'S ANSWER says that SCHOSTAREZ teaches that 5-fluoro minoxidil "is admixed with 5 alpha reductase inhibitor (i.e. finasteride) beneficially for treating alopecia, seecolumn 3, lines 49-57." EXAMINER'S ANSWER at 10. The cited text, however, merely confirms the teaching of the other references that combining minoxidil with a penetration enhancer risks precipitating cardiac side-effects. It says, "The invention also relates to compounds as described in Formula I, and combinations with antiinflammatories (steroidal and non-steroidal), androgen receptor blockers, 5α-reductase inhibitors, and -blockers for the treatment of cardiovascular disorders, such as hypertension, congestive heart failure, and angina, peripheral vascular disorders, and the treatment of alopecia." Id. at col. 3, lines 49-55. Similarly, SCHOSTAREZ at col. 4, lines 45-50 simply says that the use of penetration enhancers

"may be beneficial." This is a suggestion to pursue further experimentation - not an enabling art reference.

ZUPAN Fails to Enable the Claimed Invention

The EXAMINER'S ANSWER argues that "the claimed subject matter is inherently met by" ZUPAN. As support, the EXAMINER'S ANSWER cites ZUPAN at column 3, lines 17 - 35. That text reads as follows:

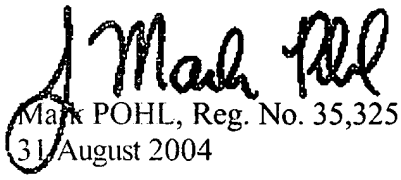
> Another object of the invention is to provide an enhancing agent which is devoid of toxic side effects.
>
> Yet another object of the invention is to provide novel compositions utilizing such novel enhancing agents, which formulations are useful for topical application.
>
> Still another object of the present invention is to provide a method for enhancing the skin penetration of bio-affecting materials.
>
> Other objects, features and advantages of the invention will be apparent to those skilled in the art upon a study of the disclosure and the appended claims.
>
> It has now been unexpectedly discovered that the aforenoted objects can be achieved by employing eucalyptol as the enhancing agent and by employing same in a composition of matter further comprising at least one bio-affecting agent. The compositions can also further comprise a topical carrier material and/or an additional penetration enhancer.

This is an invitation experiment. It fails, however, to teach minoxidil, nor 5α-reductase inhibitor, nor skin penetration enhancer, nor penetration to a depth of hair bulbs. *See* Knowles, W.R., RULE 132 DECLARATION (5 Feb. 2001).

SUMMARY

Applicant respectfully believes that the rejections must each be reversed as a matter of law.

Respectfully submitted,



Mark POHL, Reg. No. 35,325
31 August 2004

PHARMACEUTICAL PATENT ATTORNEYS, LLC
55 Madison Avenue, 4th floor (P 4014)
Morristown, NJ 07960-7397 USA

Direct: *Mark.Pohl@LicensingLaw.com*
☎ +1 (973) 984-0076

mbc:mp

Enclosures:
In re Knowles, Docket No. Misc. 767 (Fed. Cir., 16 June 2004)
MERRIAM WEBSTER'S COLLEGIATE DICTIONARY (10th ed.) page 1309
W.R. KNOWLES, SUPPLEMENTAL DECLARATION at 1 (25 April 2001)

SD:\Knowltech\Hair Loss\09.619,142 Reply Brief (30 Aug. 2004).doc

ENCLOSURES

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Official Caption[1]

Miscellaneous Docket No. 767

IN RE W. ROY KNOWLES, M.D.,

Petitioner.

On Writ of Mandamus from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences, in 09/619,142.

Authorized Abbreviated Caption[2]

IN RE KNOWLES, MISC. 767

[1] Required for use on petitions, formal briefs and appendices, court opinions, and dispositive court orders. FRAP 12(a); 32(a).

[2] Authorized for use only on items not requiring the Official Caption as listed in note 1.

NOTE: Pursuant to Fed. Cir. R. 47.6, this order is not citable as precedent. It is a public order.

United States Court of Appeals for the Federal Circuit

MISCELLANEOUS DOCKET NO. 767

IN RE W. ROY KNOWLES, M.D.,

Petitioner.

ON PETITION FOR WRIT OF MANDAMUS

Before RADER, Circuit Judge.

ORDER

W. Roy Knowles, M.D. petitions for a writ of mandamus to direct the examiner of his patent application to forward Knowles' appeal brief to the Board of Patent Appeals and Interferences.

About one year ago, Knowles filed a similar mandamus petition complaining that the examiner was thwarting his attempts to appeal to the Board. In our order denying the mandamus petition, we stated that the Director had informed Knowles of the steps he should take to obtain Board review. He followed those instructions, but now informs us that the examiner has not taken any action.

Upon consideration thereof,

IT IS ORDERED THAT:

The Director is directed to respond within 60 days.

5/6/04
Date

Randall R. Rader
Circuit Judge

cc: J. Mark Pohl, Esq.
John Whealan, Esq.

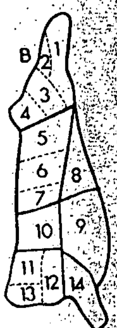
s5

Merriam-Webster's Collegiate® Dictionary

TENTH EDITION

Merriam-Webster, Incorporated
Springfield, Massachusetts, U.S.A.

...ised or
...L
...asour, fr.
(14c) : a
...NF avant-
...warder to
...most part,
...eotape re-
...ar (i.e., the
...wish calen-



...sale cuts: 1 leg, ...1 rib, 5 breast, 6 ...nk; 8 retail cuts: 2 heel of round, ...p roast, 5 sirloin ...chops, 7 kidney ..., 9 breast, 10 rib ...e steak, 12 arm ...oulder roast, 14 ...eshank

...ion of (the thrust

...he product of the ...r included angle, ...whose direction is ...move along c when

...zation of a system ...se a commutative ...ed under multipli- ...for which multipli- ...d is commutative, ... + cB and (c + d)A ...A) where A, B are

...vectors that for the ...y the diagonal of a ...s being added ...eidenai to know — ...llections of hymns, ...earliest Hindu sacred

...an Australian lady- ...tries to control scale

...lit., end of the Veda, ...); an orthodox sys- ...qualified monism the ...and the liberation of ...-\ n — Ve·dan·tist

...or relating to the Ve-

...da hunter] (1681) : a

...ancient race of south- ...chocolate-brown skin

...eletta, prob. fr. Sp vela ...o wake, watch, fr. vigil ...ed sentinel stationed in

...the Vedas, the language ...nd culture between 1500

...like the letter V. 2 : the

...announcer of a program

...] (1949) : VICE PRESIDENT

¹veer \'vir\ *vt* [ME *veren*, of LG or D origin; akin to MD *vieren* to slacken, MLG *vīren*] (15c) : to let out (as a rope)

²veer *vb* [MF *virer*, fr. OF, to throw with a twisting motion, perh. modif. of L *vibrare* to wave, propel suddenly — more at VIBRATE] *vi* (1582) **1** *of the wind* : to shift in a clockwise direction — compare BACK **2** : to change direction or course **3** : to wear ship ~ *vt* : to direct to a different course; *specif* : WEAR 7 ***syn*** see SWERVE — **veer·ing·ly** \-iŋ-lē\ *adv*

³veer *n* (1611) : a change in course or direction ⟨a ~ to the right⟩

vee·ry \'vir-ē\ *n, pl* **veeries** [prob. imit.] (1838) : a thrush (*Catharus fuscescens*) common in the eastern U.S.

veg \'vej\ *n, pl* **veg** (1918) *chiefly Brit* : VEGETABLE

Ve·ga \'vē-gə, 'vā-\ *n* [NL, fr. Ar (*al-Nasr*) *al-Wāqi'*, lit., the falling (vulture)] : a star of the first magnitude that is the brightest in the constellation Lyra

ve·gan \'vē-gən *also* 'vā- *also* 've-jən *or* -ˌjan\ *n* [by contr. fr. *vegetarian*] (1944) : a strict vegetarian who consumes no animal food or dairy products; *also* : one who abstains from using animal products (as leather) — **ve·gan·ism** \'vē-gə-ˌni-zəm, 'vā-gə-, 've-jə-\ *n*

¹veg·e·ta·ble \'vej-tə-bəl, 've-jə-\ *adj* [ME, fr. ML *vegetabilis* vegetative, fr. *vegetare* to grow, fr. L, to animate, fr. *vegetus* lively, fr. *vegēre* to enliven — more at WAKE] (15c) **1 a** : of, relating to, constituting, or growing like plants **b** : consisting of plants : VEGETATIONAL **2** : made or obtained from plants or plant products **3** : resembling or suggesting a plant (as in inertness or passivity)

²vegetable *n* (1582) **1** : PLANT 1b **2** : a usu. herbaceous plant (as the cabbage, bean, or potato) grown for an edible part that is usu. eaten as part of a meal; *also* : such edible part **3** : a human being whose mental and physical functioning is severely impaired (as from accident or disease)

vegetable ivory *n* (1842) **1** : the hard white opaque endosperm of the ivory nut that takes a high polish and is used as a substitute for ivory **2** : IVORY NUT

vegetable marrow *n* (1816) : any of various smooth-skinned elongated summer squashes with creamy white to deep green skins

vegetable oil *n* (1797) : an oil of plant origin; *esp* : a fatty oil from seeds or fruits

vegetable oyster *n* (ca. 1818) : SALSIFY

vegetable pear *n* (1887) : CHAYOTE

vegetable wax *n* (1815) : a wax of plant origin secreted commonly in thin flakes by the walls of epidermal cells

veg·e·ta·bly \'vej-tə-blē, 've-jə-\ *adv* (1651) : in the manner of or like a vegetable

veg·e·tal \'ve-jə-tᵊl\ *adj* [ML *vegetare* to grow] (15c) **1** : VEGETABLE **2** : VEGETATIVE **3** : of or relating to the vegetal pole of an egg or to that part of an egg from which the endoderm normally develops ⟨~ blastomeres⟩

vegetal pole *n* (1896) : the point on the surface of an egg that is diametrically opposite to the animal pole and usu. marks the center of the protoplasm containing more yolk, dividing more slowly and into larger blastomeres than that about the animal pole, and giving rise to the hypoblast of the embryo

¹veg·e·tar·i·an \ˌve-jə-'ter-ē-ən\ *n* [²*vegetable* + *-arian*] (1839) **1** : one who believes in or practices vegetarianism **2** : HERBIVORE

²vegetarian *adj* (1849) **1** : of or relating to vegetarians **2** : consisting wholly of vegetables, fruits, and sometimes eggs or dairy products ⟨a ~ diet⟩

veg·e·tar·i·an·ism \-ē-ə-ˌni-zəm\ *n* (ca. 1851) : the theory or practice of living on a diet made up of vegetables, fruits, grains, nuts, and sometimes eggs or dairy products

veg·e·tate \'ve-jə-ˌtāt\ *vb* **-tat·ed; -tat·ing** [ML *vegetatus*, pp. of *vegetare* to grow] *vi* (1605) **1 a** : to grow in the manner of a plant; *also* : to grow exuberantly or with proliferation of fleshy or warty outgrowths **b** : to produce vegetation **2** : to lead a passive existence without exertion of body or mind ~ *vt* : to establish vegetation in or on

veg·e·ta·tion \ˌve-jə-'tā-shən\ *n* (1564) **1** : the act or process of vegetating **2** : inert existence **3** : plant life or total plant cover (as of an area) **4** : an abnormal growth upon a body part — **veg·e·ta·tion·al** \-shnəl, -shə-nᵊl\ *adj*

veg·e·ta·tive \'ve-jə-ˌtā-tiv\ *adj* (14c) **1 a (1)** : growing or having the power of growing **(2)** : of, relating to, or engaged in nutritive and growth functions as contrasted with reproductive functions ⟨a ~ nucleus⟩ **b** : promoting plant growth ⟨the ~ properties of soil⟩ **c** : of, relating to, or involving propagation by nonsexual processes or methods **2** : relating to, composed of, or suggesting vegetation ⟨~ cover⟩ **3** : of or relating to the division of nature comprising the plant kingdom **4** : affecting, arising from, or relating to involuntary bodily functions **5** : VEGETABLE 3 — **veg·e·ta·tive·ly** *adv* — **veg·e·ta·tive·ness** *n*

ve·gete \və-'jēt\ *adj* [L *vegetus* — more at VEGETABLE] (1639) *archaic* : LIVELY, HEALTHY

veg·gie *also* **veg·ie** \'ve-jē\ *n* [by shortening & alter.] (1955) **1** : VEGETABLE **2** *slang* : VEGETARIAN

veg out \'vej-\ *vi* **vegged out; veg·ging out** [short for *vegetate*] (1980) : to spend time idly or passively

ve·he·mence \'vē-ə-mən(t)s\ *n* (15c) : the quality or state of being vehement : INTENSITY

ve·he·ment \-mənt\ *adj* [ME, fr. MF, fr. L *vehement-*, *vehemens*, *vemens*] (15c) : marked by forceful energy : POWERFUL ⟨a ~ wind⟩: as **a** : intensely emotional : IMPASSIONED, FERVID ⟨~ patriotism⟩ **b (1)** : deeply felt ⟨a ~ suspicion⟩ **(2)** : forcibly expressed ⟨~ denunciations⟩ **c** : bitterly antagonistic ⟨a ~ debate⟩ — **ve·he·ment·ly** *adv*

ve·hi·cle \'vē-ə-kəl *also* 'vē-ˌhi-kəl\ *n* [F *véhicule*, fr. L *vehiculum* carriage, conveyance, fr. *vehere* to carry — more at WAY] (1612) **1 a** : an inert medium (as a syrup) in which a medicinally active agent is administered **b** : any of various media acting usu. as solvents, carriers, or binders for active ingredients or pigments **2** : an agent of transmission : CARRIER **3** : a medium through which something is expressed, achieved, or displayed **4** : a means of carrying or transporting something : CONVEYANCE: as **a** : MOTOR VEHICLE **b** : a piece of mechanized equipment

ve·hic·u·lar \vē-'hi-kyə-lər\ *adj* (1616) **1 a** : of, relating to, or designed for vehicles and esp. motor vehicles **b** : transported by vehicle **c** : caused by or resulting from the operation of a vehicle ⟨~ homicide⟩ **2** : serving as a vehicle

V-8 \'vē-'āt\ *n* (1942) : an internal combustion engine having two banks of four cylinders each with the banks at an angle to each other; *also* : an automobile having such an engine

¹veil \'vā(ə)l\ *n* [ME *veile*, fr. ONF, fr. L *vela*, pl. of *velum* sail, awning, curtain] (13c) **1 a** : a length of cloth worn by women as a covering for the head and shoulders and often esp. in Eastern countries for the face; *specif* : the outer covering of a nun's headdress **b** : a length of veiling or netting worn over the head or face or attached for protection or ornament to a hat or headdress **c** : any of various liturgical cloths; *esp* : a cloth used to cover the chalice **2** : the cloistered life of a nun **3** : a concealing curtain or cover of cloth **4** : something that hides or obscures like a veil **5** : a covering body part or membrane: as **a** : VELUM **b** : CAUL

²veil *vt* (14c) : to cover, provide, obscure, or conceal with or as if with a veil ~ *vi* : to put on or wear a veil

veiled \'vā(ə)ld\ *adj* (1593) **1 a** : having or wearing a veil or a concealing cover ⟨a ~ hat⟩ **b** : characterized by a softening tonal distortion **2** : obscured as if by a veil : DISGUISED ⟨~ threats⟩

veil·ing \'vā-liŋ\ *n* (14c) **1** : VEIL **2** : any of various light sheer fabrics

¹vein \'vān\ *n* [ME *veine*, fr. OF, fr. L *vena*] (14c) **1 a** : a narrow water channel in rock or earth or in ice **b (1)** : LODE 2, 3 **(2)** : a bed of useful mineral matter **2** : BLOOD VESSEL; *esp* : any of the tubular branching vessels that carry blood from the capillaries toward the heart **3 a** : any of the vascular bundles forming the framework of a leaf **b** : any of the thickened cuticular ribs that serve to stiffen the wings of an insect **4** : something suggesting veins (as in marble) **5 a** : a distinctive mode of expression : STYLE **b** : a pervasive element or quality : STRAIN **c** : a line of thought or action **6 a** : a special aptitude : TALENT **b** : a usu. transitory and casually attained mood **c** : top form : FETTLE — **vein·al** \'vā-nᵊl\ *adj*

²vein *vt* (1502) : to pattern with or as if with veins

veined \'vānd\ *adj* (ca. 1529) : patterned with or as if with veins : having venation : STREAKED ⟨a ~ leaf⟩ ⟨~ marble⟩ ⟨~ cheese⟩

vein·er \'vā-nər\ *n* (1895) : a small V gouge used in wood carving

vein·ing \'vā-niŋ\ *n* (1826) : a pattern of veins : VENATION

vein·let \'vān-lət\ *n* (1831) : a small vein

veiny \'vā-nē\ *adj* (1611) : full of veins : noticeably veined

ve·la·men \və-'lā-mən\ *n, pl* **ve·lam·i·na** \-'la-mə-nə\ [NL, fr. L, covering, fr. *velare* to cover, fr. *velum* curtain] (1882) : the thick corky epidermis of aerial roots of an epiphytic orchid that absorbs water from the atmosphere

ve·lar \'vē-lər\ *adj* [NL *velaris*, fr. *velum*] (1876) **1** : formed with the back of the tongue touching or near the soft palate ⟨the ~ \k\ of \'kül\ *cool*⟩ **2** : of, forming, or relating to a velum and esp. the soft palate — **velar** *n*

ve·lar·i·um \vi-'lar-ē-əm, -'ler-\ *n, pl* **-ia** \-ē-ə\ [L, fr. *velum* curtain] (1834) : an awning over an ancient Roman theater or amphitheater

ve·lar·i·za·tion \ˌvē-lə-rə-'zā-shən\ *n* (1915) **1** : the quality or state of being velarized **2** : an act or instance of velarizing

ve·lar·ize \'vē-lə-ˌrīz\ *vt* **-ized; -iz·ing** (1915) : to modify (as the \l\ of \'pül\ *pool*) by a simultaneous velar articulation

Vel·cro \'vel-(ˌ)krō\ *trademark* — used for a closure consisting of a piece of fabric of small hooks that sticks to a corresponding fabric of small loops

veld *or* **veldt** \'velt, 'felt\ *n* [Afrik *veld*, fr. D, field; akin to OE *feld* field] (1835) : a grassland esp. of southern Africa usu. with scattered shrubs or trees

ve·li·ger \'vē-lə-jər, 've-\ *n* [NL, fr. *velum* + *-ger* bearing, fr. *gerere* to bear] (1877) : a larval mollusk in the stage when it has developed the velum

vel·le·i·ty \ve-'lē-ə-tē, və-\ *n, pl* **-ties** [NL *velleitas*, fr. L *velle* to wish, will — more at WILL] (1618) **1** : the lowest degree of volition **2** : a slight wish or tendency : INCLINATION

¹vel·lum \'ve-ləm\ *n* [ME *velim*, fr. MF *veelin*, fr. *veelin*, adj., of a calf, fr. *veel* calf — more at VEAL] (15c) **1** : a fine-grained unsplit lambskin, kidskin, or calfskin prepared esp. for writing on or for binding books **2** : a strong cream-colored paper

²vellum *adj* (1565) **1** : of, resembling, or bound in vellum **2** : slightly rough ⟨paper with a ~ finish⟩

ve·lo·ce \vā-'lō-(ˌ)chā\ *adv or adj* [It, fr. L *veloc-*, *velox*] (ca. 1823) : in a rapid manner — used as a direction in music

ve·lo·cim·e·ter \ˌvē-lō-'si-mə-tər, ˌve-\ *n* [*velocity* + *-meter*] (1842) : a device for measuring speed (as of fluid flow or sound)

ve·loc·i·pede \və-'lä-sə-ˌpēd\ *n* [F *vélocipède*, fr. L *veloc-*, *velox* + *ped-*, *pes* foot — more at FOOT] (1818) : a lightweight wheeled vehicle propelled by the rider: as **a** *archaic* : BICYCLE **b** : TRICYCLE **c** : a 3-wheeled railroad handcar

ve·loc·i·ty \və-'lä-sə-tē, -'läs-tē\ *n, pl* **-ties** [MF *velocité*, fr. L *velocitat-*, *velocitas*, fr. *veloc-*, *velox* quick; prob. akin to L *vegēre* to enliven — more at WAKE] (ca. 1550) **1 a** : quickness of motion : SPEED ⟨the ~ of sound⟩ **b** : rapidity of movement ⟨[my horse's] strong suit is grace & personal comeliness, rather than ~ —Mark Twain⟩ **c** : speed imparted to something ⟨the power pitcher relies on ~ —Tony Scherman⟩ **2** : the rate of change of position along a straight line with respect to time : the derivative of position with respect to time **3 a** : rate of occurrence or action : RAPIDITY ⟨the ~ of historical change —R. J. Lifton⟩ ⟨the narrative leaps from one frantic episode to another with impressive ~ —James Atlas⟩ **b** : rate of turnover ⟨the ~ of money⟩

ve·lo·drome \'vē-lə-ˌdrōm, 've-, 'vā-\ *n* [F *vélodrome*, fr. *vélo* cycle (short for *vélocipède*) + *-drome*] (1895) : a track designed for cycling

ve·lour *or* **ve·lours** \və-'lu̇r\ *n, pl* **velours** \-'lu̇rz\ [F *velours* velvet, fr. MF *velours*, *velour*, fr. OF *velous*, fr. OProv *velos*, fr. L ...*losus* shaggy, fr. *villus* shaggy hair — more at VELVET] (ca. 1706) ...

\ə\ abut \ᵊ\ kitten, F table \ər\ further \a\ ash \ā\ ace \ä\ mop, mar
\au̇\ out \ch\ chin \e\ bet \ē\ easy \g\ go \i\ hit \ī\ ice \j\ job
\ŋ\ sing \ō\ go \ȯ\ law \ȯi\ boy \th\ thin \t͟h\ the \ü\ loot \u̇\ foot
\y\ yet \zh\ vision \à, k̟, ⁿ, œ, œ̄, ue, ue̅, ʸ\ see Guide to Pronunciation

MERRIAM-WEBSTER INC.
SPRINGFIELD, MA 01102

IN THE UNITED STATES PATENT OFFICE

Inventor : W. Roy KNOWLES, M.D.
Filing Date: 19 July 2000
Ser. No.: 09/619,142
Art Unit: 1614
Examiner: Vickie KIM

SUPPLEMENTAL DECLARATION UNDER RULE 1.132

1) I am the inventor of record for the captioned patent application. I make this Declaration under 37 Code of Federal Regulations Rule 1.132.

2) Bazzano. I have read Bazzano, United States Patent No. 5,183,817. Bazzano teaches that PEG-ethanol mixtures are inert cosmetic carrier vehicles. Bazzano says, at column 19, lines 66-68, that "lotions may be prepared using various forms of alcohols or other solubilizers such as glycols or esters." Bazzano here simply reiterates the conventional wisdom that glycols (such as PEG) ethanol are useful "solubilizers"; that is, as an inert diluent or vehicle, without skin penetration efficacy on their own.

3) Bazzano discusses using PEG-ethanol as an inert "vehicle" and as a "placebo." Bazzano at col. 21-24 and claims 23-24. Researchers skilled in the art recognize these terms indicate compounds that have no skin permeability or skin penetration efficacy on their own.

4) Bazzano's Example I, at column 24, teaches using PEG-ethanol as the vehicle for topical minoxidil administration. This formulation appears simply to have been copied from that for Pharmacia & Upjohn's formulation for their commercially-available ROGAINE® product, which uses PEG-ethanol as the vehicle.

5) Mikulak. I have reviewed the abstract provided by the Examiner. I find it uncontroversial. The abstract appears to describe a test of a new skin penetration agent called TPDS. The abstract uses PEG-ethanol (50:50), apparently as the experimental control, and compares it against TPDS, a "commonly used skin penetration enhancer" and oral administration. This abstract confirms that Mikulak et al. consider PEG-ethanol not a skin penetration agent; if it were, Mikulak would have needed to use a different, inert compound as the experimental control.

6) Rajadhyaksha. I have reviewed United States Patent No. 5,482,965. It teaches transdermal drug delivery agents useful for the delivery of drugs through the skin and into the systemic blood circulation. The reference highlights the claimed compounds' systemic safety, such as the systemic safety of the breakdown products.

7) This is supported by the examples. Example 32 shows a standard skin-penetration activity assay. The results of Example 32 show that the disclosed compounds do indeed work as exceptional skin permeability enhancers, carrying drug compounds entirely through the tested skin samples. This indicates that the same compounds, if used *in vivo*, would provide excellent drug delivery completely through the skin and into the systemic blood circulation.

8) The reference teaches using 5-amino-5-ethyl-2-(3-heptyl)-1,3-dioxane ("A5A") as a skin permeability enhancer. Examples 28-30 disclose using A5A at a 5% concentration. The drugs of Examples 28 and 30 are only used systemically. Thus, I conclude that the 5% A5A concentration used effects systemic delivery of the drugs. Thus, I conclude that Example 29, a progesterone skin patch, effects systemic delivery of progesterone through the skin and into the systemic blood circulation. Example 29 is therefore a birth control skin patch.

9) Similarly, Example 18 teaches administering minoxidil using 5% A5A. As mentioned above, the reference teaches 5% A5A is useful for the administration of drugs through the skin into the systemic blood circulation. Example 18 does nothing to

teach how to deliver minoxidil to the level of the hair bulbs, nor how to avoid delivery of the minoxidil into the systemic blood circulation, nor how to avoid cardiovascular side effects of such systemic drug delivery.

10) Therefore, nothing in the reference enables the claimed invention. Specifically, nothing enables one of skill in the art to practice "penetration enhancer present in a concentration sufficient to aid said active compound in penetrating the skin surface to a depth of approximately the depth of hair bulbs."

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

W. Roy Knowles M.D.

W. Roy KNOWLES, M.D.
April 25, 2001

X:\pohlm\Knowles\Supplemental Declaration